

(h) inhibiting an increase of an elevated level of hydroxyproline in the kidney;

(i) obtainable by immunizing a mouse with human CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs;

(j) obtainable by immunizing a hamster with mouse CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs;

(k) obtainable by immunizing a rat with mouse CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs;

(l) obtainable by immunizing a mouse with human CTGF or a portion thereof, reactive to human, mouse and rat CTGFs and inhibiting binding of human CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573);

(m) obtainable by immunizing a rat with mouse CTGF or a portion thereof, reactive to human, mouse and rat CTGFs and inhibiting binding of mouse CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573); and,

(n) obtainable by immunizing a hamster with mouse CTGF or a portion thereof, and reactive to human, mouse and rat CTGFs and inhibiting binding of mouse CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573).

105. (New) The monoclonal antibody or a portion thereof according to claim 104, wherein said monoclonal antibody is produced by a hybridoma identified by an international deposit accession No. FERM BP-6208.

106. (New) The monoclonal antibody or a portion thereof according to claim 104, wherein said monoclonal antibody comprises a property substantially equivalent to that of a monoclonal antibody produced by a hyhridoma identified by an international deposit accession No. FERM BP-6208.

107. (New) The monoclonal antibody or a portion thereof according to claim 104, wherein said monoclonal antibody is produced by a hybridoma identified by an international deposit accession No. FERM BP-6209.

108. (New) The monoclonal antibody or a portion thereof according to claim 104, wherein said monoclonal antibody comprises a property substantially equivalent to that of a monoclonal

antibody produced by a hybridoma identified by an international deposit accession No. FERM BP-6209.

109. (New) A human monoclonal antibody or a portion thereof, reactive to human CTGF.

110. (New) A human monoclonal antibody or a portion thereof according to claim 109, which comprises a property selected from the group consisting of:

(a) inhibiting binding of human CTGF to human kidney-derived fibroblast cell line 293-T (ATCC CRL1573);

(b) inhibiting binding of human CTGF to any of rat kidney-derived fibroblast cell line NRK-49F (ATCC CRL-1570), human osteosarcoma-derived cell line MG-63 (ATCC CRL-1427), or human lung-derived fibroblasts;

(c) inhibiting the cell proliferation of rat kidney-derived fibroblast cell line NRK49F (ATCC CRL-1570) induced by a stimulus with human or mouse CTGF; and,

(d) inhibiting an increase of an elevated level of hydroxyproline in kidney.

111. (New) The human monoclonal antibody or a portion thereof according to claim 109, wherein said human monoclonal antibody is derived from a non-human transgenic mammal which is capable of producing a human antibody.

112. (New) The human monoclonal antibody or a portion thereof according to claim 109, wherein said human monoclonal antibody is derived from a transgenic mouse which is capable of producing a human antibody.

113. (New) The human monoclonal antibody or a portion thereof according to claim 109, wherein a V-region DNA encoding a heavy chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DP-5, DP-38, DP-65 and DP-75.

114. (New) The human monoclonal antibody or a portion thereof according to claim 109, wherein a V-region DNA encoding a light chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DPK1, DPK9, DPK12 and DPK24.

115. (New) The human monoclonal antibody or a portion thereof according to claim 109, wherein a V-region DNA encoding a heavy chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DP-5, DP-38, DP-65 and DP-75, and wherein a V-region DNA encoding a light chain variable region of said human monoclonal antibody is derived from a gene segment selected from the group consisting of DPK1, DPK9, DPK12 and DPK24.

116. (New) The human monoclonal antibody or a portion thereof according to claim 109, wherein an amino acid sequence of a heavy chain variable region of said human monoclonal antibody comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid positions 21 to 120 of the amino acid sequence of SEQ ID NO:6;
- (b) the amino acid positions 21 to 120 of the amino acid sequence of SEQ ID NO: 6, wherein one or more amino acids are deleted, substituted, inserted or added;
- (c) the amino acid positions 21 to 118 of the amino acid sequence of SEQ ID NO: 8;
- (d) the amino acid positions 21 to 118 of the amino acid sequence of SEQ ID NO: 8, wherein one or more amino acids are deleted, substituted, inserted or added;
- (e) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 10;
- (f) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 10, wherein one or more amino acids are deleted, substituted, inserted or added;
- (g) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 12;
- (h) the amino acid positions 21 to 116 of the amino acid sequence of SEQ ID NO: 12, wherein one or more amino acids are deleted, substituted, inserted or added;
- (i) the amino acid positions 21 to 117 of the amino acid sequence of SEQ ID NO: 14; and
- (j) the amino acid positions 21 to 117 of the amino acid sequence of SEQ ID NO: 14, wherein one or more amino acids are deleted, substituted, inserted or added.

117. (New) The human monoclonal antibody or a portion thereof according to claim 109, wherein an amino acid sequence of alight chain variable region of said human monoclonal antibody comprises an amino acid sequence selected from the group consisting of:

- (a) the amino acid positions 21 to 120 of the amino acid sequence of SEQ ID NO: 16;
- (b) the amino acid positions 21 to 120 of the amino acid sequence of SEQ ID NO: 16, wherein one or more amino acids are deleted, substituted, inserted or added;

(c) the amino acid positions 21 to 121 of the amino acid sequence of SEQ ID NO:18;

(d) the amino acid positions 21 to 121 of the amino acid sequence of SEQ ID NO: 18, wherein one or more amino acids are deleted, substituted, inserted or added;

(e) the amino acid positions 23 to 117 of the amino acid sequence of SEQ ID NO: 20;

(f) the amino acid positions 23 to 117 of the amino acid sequence of SEQ ID NO: 20, wherein one or more amino acids are deleted, substituted, inserted or added;

(g) the amino acid positions 17 to 111 of the amino acid sequence of SEQ ID NO: 22;

(h) the amino acid positions 17 to 111 of the amino acid sequence of SEQ ID NO: 22, wherein one or more amino acids are deleted, substituted, inserted or added;

(i) the amino acid positions 23 to 118 of the amino acid sequence of SEQ ID NO: 24; and,

(j) the amino acid positions 23 to 118 of the amino acid sequence of SEQ ID NO: 24, wherein one or more amino acids are deleted, substituted, inserted or added.

B1
cm: X
DRAFT 6/2000

118. (New) The human monoclonal antibody or a portion thereof according to claim 109, which is produced by a hybridoma identified by an international deposit accession numbers selected from the group consisting of FERM BP-6535, FERM BP-6598, FERM BP-6599 and FERM-BP-6600.

119. (New) The human monoclonal antibody or a portion thereof according to claim 109, which comprises a property substantially equivalent to that of a monoclonal antibody produced by a hybridoma identified by an international deposit accession numbers selected from the group consisting of FERM BP-6535, FERM BP-6598, FERM BP-6599 and FERM-BP-6600.

120. (New) The human monoclonal antibody or a portion thereof according to claim 109, which is non-reactive to an antigen antibody complex of human CTGF and a monoclonal antibody produced by a hybridoma identified by an international deposit accession numbers selected from the group consisting of FERM BP-6535, FERM BP6598, FERM BP-6599 and FERM BP-6600.

Sub C2

121. (New) A cell producing the monoclonal antibody according to claim 104.

122. (New) A cell producing the human monoclonal antibody according to claim 109.

Sub C 3
123. (New) The cell according to claim 121, wherein said cell is a hybridoma obtainable by fusing a mammalian myeloma cell with a mammalian B cell which is capable of producing the monoclonal antibody.

124. (New) The cell according to claim 122, wherein said cell is a hybridoma obtainable by fusing a mammalian myeloma cell with a mammalian B cell which is capable of producing the monoclonal antibody.

B1 Cn X
125. (New) The cell according to claim 121, wherein said cell is a genetically engineered cell transformed by either one or both of the DNAs encoding a heavy chain and light chain of the monoclonal antibody.

126. (New) The cell according to claim 122, wherein said cell is a genetically engineered cell transformed by either one or both of the DNAs encoding a heavy chain and light chain of the human monoclonal antibody.

127. (New) A hybridoma identified by an international deposit accession numbers selected from the group consisting of FERM BP-6535, FERM BP-6598, FERM BP-6599, FERM BP-6600, FERM BP-6208 and FERM BP-6209.

Sub C 4
128. (New) An antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized.

Sub C 5
129. (New) The antibody-immobilized insoluble carrier according to claim 128, wherein said insoluble carrier is selected from the group consisting of plates, test tubes, tubes, beads, balls, filters and membranes.

130. (New) The antibody-immobilized insoluble carrier according to claim 128, wherein said insoluble carrier is a filter or membrane, or that used for affinity column chromatography.

131. (New) A labeled antibody which is prepared by labeling the monoclonal antibody according to claim 104 with a labeling agent capable of providing a detectable signal by itself or together with other substances.

132. (New) The labeled antibody according to claim 131, wherein said labeling agent is an enzyme, fluorescent substance, chemiluminescent substance, biotin, avidin, or radioisotope.

133. (New) A kit for detecting or assaying mammalian CTGF, comprising the monoclonal antibody according to claim 104.

134. (New) A kit for detecting or assaying mammalian CTGF comprising an antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized.

135. (New) A kit for detecting or assaying mammalian CTGF comprising a labeled antibody which is prepared by labeling the monoclonal antibody according to claim 104 with a labeling agent capable of providing a detectable signal by itself or together with other substances.

136. (New) A method for detecting or assaying mammalian CTGF by an immunoassay, comprising at least the following steps of (a) and (b):

(a) reacting a sample with an antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized; and,

(b) reacting a labeled antibody which is prepared by labeling the monoclonal antibody according to claim 104 with a labeling agent capable of providing a detectable signal by itself or together with other substances, with an antigen-antibody complex formed by binding mammalian CTGF in said sample to the antibody-immobilized insoluble carrier.

137. (New) A method for detecting or assaying mammalian CTGF by an immunoassay, comprising at least the following steps of (a) and (b):

(a) reacting a sample with a labeled antibody which is prepared by labeling the monoclonal antibody according to claim 104 with a labeling agent capable of providing a detectable signal by itself

or together with other substances; and,

(b) reacting an antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized, with the antigen-antibody complex formed by binding said labeled antibody and mammalian CTGF in said sample.

138. (New) A method for detecting or assaying mammalian CTGF by an immunoassay, comprising at least the following step of (a):

(a) reacting a mixture comprising an antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized, a labeled antibody which is prepared by labeling the monoclonal antibody according to claim 104 with a labeling agent capable of providing a detectable signal by itself or together with other substances, and a sample.

139. (New) A method for detecting or assaying mammalian CTGF by an immunoassay, comprising at least the following step of (a):

(a) reacting a sample and a mammalian CTGF standard labeled with a labeling agent capable of providing a detectable signal by itself or together with other substances, with an antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized.

140. (New) A method for detecting or assaying mammalian CTGFs by an immunoassay, comprising at least the following steps of (a) and (b):

(a) reacting the monoclonal antibody according to claim 104 with a mixture comprising a sample and a mammalian CTGF standard labeled with a labeling agent capable of proving a detectable signal by itself or together with other substances; and,

(b) reacting a mammalian antiserum reactive to said monoclonal antibody with the antigen-antibody complex formed by binding mammalian CTGF in said sample or said labeled mammalian CTGF standard and said monoclonal antibody.

141. (New) A method for detecting or assaying mammalian CTGFs by an immunoassay, comprising at least the following steps of any of (a) to (c):

(a) reacting the monoclonal antibody according to claim 104 with a sample;

(b) reacting a mammalian CTGF standard labeled with a labeling agent capable of providing a

detectable signal by itself or together with other substances with a reaction product resulted from the reaction in step (a); and,

(c) reacting a mammalian antiserum reactive to said monoclonal antibody with the antigen-antibody complex formed by binding mammalian CTGF in said sample or said labeled mammalian CTGF standard, and said monoclonal antibody.

Sub C
142. (New) A kit for separating or purifying mammalian CTGF, comprising an antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized.

B1 X Chem 250
143. (New) A method for separating or purifying mammalian CTGF, comprising using affinity chromatography with an antibody-immobilized insoluble carrier on which the monoclonal antibody according to claim 104 is immobilized.

144. (New) The purification method for mammalian CTGF according to claim 143, wherein said affinity chromatography is affinity column chromatography.

145. (New) A transgenic mouse in which DNA encoding human CTGF is integrated into an endogenous gene locus.

146. (New) A rat CTGF comprising an amino acid sequence of, or substantially equivalent to an amino acid sequence of SEQ ID NO: 2.

147. (New) A DNA encoding a rat CTGF, which is selected from the group consisting of:

- (a) the DNA encoding the amino acid sequence of SEQ ID NO: 2; or
- (b) the DNA comprising nucleotide sequence in the position of 213 to 1256 of SEQ ID NO: 1.

148. (New) A pharmaceutical composition comprising the human monoclonal antibody or a portion thereof according to claim 109 and a pharmaceutically acceptable carrier.

149. (New) The pharmaceutical composition according to claim 148, for any one selected from the group consisting of:

- (a) inhibiting proliferation of cells capable of proliferating by a stimulus with CTGF;
- (b) treating or preventing a disease accompanied by proliferation of cells capable of proliferating by a stimulus with CTGF;
- (c) inhibiting proliferation of cells capable of proliferating by a stimulus with CTGF, wherein said proliferation is cell proliferation in a tissue selected from the group consisting of brain, neck, lung, heart, liver, pancreas, kidney, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue and blood vessels;
- (d) treating or preventing a disease accompanied by proliferation of cells capable of proliferating by a stimulus with CTGF, wherein said proliferation is cell proliferation in a tissue selected from the group consisting of brain, neck, lung, heart, liver, pancreas, kidney, stomach, large intestine, small intestine, duodenum, bone marrow, uterus, ovary, testis, prostate gland, skin, mouth, tongue and blood vessels;
- (e) treating or preventing a disease accompanied by proliferation of cells capable of proliferating by a stimulus with CTGF, wherein disease is further accompanied by tissue fibrosis; and
- (f) treating or preventing a tissue fibrosis is tissue fibrosis in lung, liver, kidney or skin.

150. (New) A pharmaceutical composition for treating or preventing a kidney disease, comprising a CTGF inhibitor or an agent for inhibiting CTGF production, and a pharmaceutically acceptable carrier.

151. (New) The pharmaceutical composition according to claim 150, wherein said inhibitor is a monoclonal antibody reactive to human CTGF.

152. (New) The pharmaceutical composition according to claim 150, wherein said disease is accompanied by tissue fibrosis.

153. (New) A pharmaceutical composition for inhibiting proliferation of cells in kidney which are capable of proliferating by a stimulus with CTGF, comprising a substance having an activity of inhibiting proliferation of said cells and a pharmaceutically acceptable carrier.